SHORT-TERM RISK FACTORS FOR SUDDEN DEATH

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The investigations described in this report have been directed at ascertaining the factors that determine the risk of sudden death within 5 years among middle-aged American men, the conditions under which sudden deaths occur, and the factors that precipitate these deaths. Such information is of great importance for the secondary prevention of sudden death and for the clinical management of patients who have heart disease.

METHODS

The investigations have been based on a 5-year prospective survey of 1839 deaths attributed to coronary heart disease among 269,755 men aged 20 to 65 years employed in the telephone industry throughout the continental United States [1] and on 1023 5-year intensive prospective observations of men aged 40 to 65. These intensive observations included repeated (one to seven times) comprehensive medical histories and examinations; reviews of activities, medications, smoking, drinking, and time budgets; determinations of blood lipids, glucose tolerance, and serum uric acid; biochemical and hematologic profiles; chest X-ray films; 12-lead electrocardiograms and 24-hour recordings of electrocardiograms; and investigations of all deaths (total 142) that occurred.[2] The subjects, from 21 white- and blue-collar industries and two labor unions in New York, New Jersey and Connecticut, included 333 selected from medical records because of features thought to indicate "high risk," and 687 designated in random samples from age cohorts of employed men in which the sudden death rates and the incidence of coronary heart disease were determined to be similar to those of comparable men nationwide. The prevalence of coronary heart disease (CHD) and hypertension, the body-build, the rate of smoking and drinking, the serum cholesterol and serum uric acid levels, and the results on glucose tolerance tests in the random samples were also comparable to those of contemporary men nationwide.[2]

FINDINGS

"Sudden Deaths," "Arrhythmic Deaths," and "Deaths in Circulatory Failure"

Three-fifths (60.4%) of 1476 deaths attributed to coronary heart disease in the nationwide survey terminated final illnesses that lasted less than 2 hours. Forty-two and five-tenths percent of these "sudden deaths" (25.7% of all deaths

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attributed to coronary heart disease) occurred in men who had not previously been known to have coronary heart disease.[1]

On the basis of information from witnesses, rescue squads, physicians, hospitals, autopsy reports (31%), electrocardiograms and electrocardiographic recordings at or shortly after the time of collapse (20.4%), and our own previous examinations, 141 of the 142 deaths among men who were intensively observed could be classified into two major categories[3]: In 82 cases (58%) the pulse ceased abruptly without prior collapse of the circulation and did not return spontaneously. The adequacy of the circulation for perfusing the brain immediately before death was indicated by the fact that the subjects were conscious (often active) or asleep and readily aroused. Electrocardiograms obtained at or shortly after the time of collapse showed ventricular fibrillation or asystole. These deaths were classified as "arrhythmic." In 59 cases (42%) the peripheral circulation collapsed gradually, although sometimes rapidly, the subject lost consciousness and was not arousable, and the blood pressure could no longer be obtained, before the pulse finally ceased. These were classified as "deaths in circulatory failure."[3]

The primary cause of "sudden death" in these men was the sudden development of a cardiac arrhythmia. All "instantaneous deaths" that occurred in less than 5 minutes were "arrhythmic." Ninety-one and three-tenths percent of deaths in less than 1 hour were "arrhythmic," 84.8% of deaths in less than 24 hours were "arrhythmic," and 23.8% of deaths in which the final illness lasted more than 24 hours were "arrhythmic."

Noncardiac "Risk Factors" for Arrhythmic Death Within 5 Years

In the random samples the presence of vascular hypertension at the initial examination was associated with a slightly enhanced risk of arrhythmic death in 5 years, the risk increasing with the severity of the hypertension; present cigarette smoking was associated with enhanced risk of both arrhythmic death and death in circulatory failure, the risk increasing with the number of cigarettes being smoked; but the presence of a serum cholesterol concentration ≥ 250 mg/dL was associated only with an enhanced risk of death in circulatory failure (caused by deaths attributed to stroke and peripheral vascular disease) (TABLE 1).

Other noncardiac factors affecting a smaller proportion of the men were associated with a relatively larger proportion of deaths. Clinical diabetes mellitus was associated with deaths of both kinds. An enhanced risk of arrhythmic death was associated with a serum uric acid concentration ≥ 8 mg/dL; clinical evidence of arteriosclerosis of vessels other than the coronary arteries (calcification or aneurysm of aorta, intermittent claudication, stroke, or transient ischemic attacks); the consumption of five or more alcoholic drinks per day; and the presence of chronic obstructive pulmonary disease with severe airway disease ($FEV_1/VC < 60\%$).

Eighty-eight and eight-tenths percent of the men in the random sample had one or more of these noncardiac "risk factors" at the initial examination; the arrhythmic death rate of the men who had none of these was lower than that of the other men in the sample.

TABLE 1

RANDOM SAMPLES:
NONCARDIAC RISK FACTORS PRESENT AT INITIAL EXAMINATION

	Men at Risk *		Deaths in 5 Years: Arrhythmic † (n=38)		Deaths in 5 Years: Circulatory Failure ‡ (n=32)	
	No.	%	No.	Rate per 100	No.	Rate per 100
All men in random samples	687	100	100	5.5	100	4.7
Hypertension						
Definite (≥ 160/95) §	201	30.0	45.9	8.4 ||	22.5	3.5
Borderline (≥140/90, but < 160/95) §	156	23.3	21.6	5.1	25.8	5.1
None	312	46.6	32.4	3.8	51.6	5.1
Now smoking cigarettes						
More than 40/day	49	7.3	19.4	14.3 #	12.9	8.2 ¶
10–39/day	140	21.0	25.0	6.4	38.7	8.6
None	479	71.7	55.5	4.2	51.6	3.3
Serum cholesterol ≥250 mg/dL	265	41.3	37.5	4.5	62.1	6.8 ¶
Clinical diabetes mellitus	33	5.1	14.7	15.2 ¶	16.7	15.2 ¶
Serum uric acid ≥8.0 mg/dL	53	8.4	25.3	15.1 #	6.2	3.8
Arteriosclerosis of aorta or peripheral or cerebral arteries	131	15.4	37.8	10.6 ¶	16.7	3.8
Now drinking >5 drinks/day	31	4.5	12.8	16.1 ¶	3.1	3.1
Chronic obstructive pulmonary disease with FEV_1/VC <60%	12	1.8	16.7	33.3 #	0.0	0.0
Men with none of the above	77	11.2	2.9	1.3	10.0	3.9

NOTE: Estimates of probability are based on Chi square analyses, with Yates correction when indicated. Estimates relate to the probability that the indicated rate of arrhythmic deaths or of deaths in circulatory failure is different from the rate among other men at risk with data on this variable.

* This column represents all of the men at risk for whom complete data were available for the variable under consideration. A small and variable number of the men in the samples (range 0 to 88) did not have complete data on each variable. The % of men at risk is the percent of men with complete data on the variable under consideration who were at risk.

† This column represents arrhythmic deaths within 5 calendar years among the men at risk. A small and variable number of men (range 0 to 6) who suffered arrhythmic deaths did not have complete data on each variable. The % of arrhythmic deaths in this column is the percent of all the arrhythmic deaths that occurred among men who had complete data on the variable under consideration. Rate per 100 is the rate of arrhythmic deaths within five years among men who had complete data on the variable under consideration.

‡ The same considerations apply for deaths in circulatory failure as for arrhythmic deaths as stated in the preceding footnote.

§ References 2 and 4.

|| $p < 0.1$.

# $p < 0.01$.

¶ $p < 0.05$.

Myocardial Disease Risk Factors for Arrhythmic Death in 5 Years

Clinical evidences of myocardial disease were, as single variables, the most potent risk factors for sudden death in 5 years. The 15.0% of men in the random samples who had definite clinical evidence of ischemic heart disease ("definite" or "probable" previous myocardial infarction, electrocardiographic evidence of old myocardial infarction, or definite clinical evidence of coronary insufficiency or angina pectoris) [2, 4] had a 5-year arrhythmic death rate of 16.5 per 100. Men with definite ischemic heart disease accounted for 44.7% of the arrhythmic deaths within 5 years. The risk of men with "probable" and "possible" ischemic heart disease was not significantly higher than that of other men with no clinical evidence of coronary heart disease, but it was three times as high as that of men with no evidence of any form of myocardial disease ($p < 0.05$) (TABLE 2).

Men with "definite" and "probable" electrocardiographic patterns of left ventricular hypertrophy (LVH),[2, 5] men with a transverse cardiac diameter on X-ray films ≥ 2 SD above the expected mean for height and weight,[2, 6] and men with definite clinical evidence of past or present congestive heart failure,[2] representing 2.4–4.6% of the men in the sample, had significantly enhanced risks of arrhythmic death (22.2–44.4 per 100) and accounted for 12.1–21.1% of the arrhythmic deaths in 5 years. Men with "possible" LVH patterns on the electrocardiogram (voltage abnormalities only) had an arrhythmic death rate not greater than that of all other men without LVH patterns, but three times as high as that of men with no evidence of myocardial disease.

One-half (49.4%) of the men in the random samples who had no clinical evidence of definite, probable, or possible myocardial disease at the initial examination experienced only 13.5% of the arrhythmic deaths in 5 years; the arrhythmic death rate among these men (1.6 per 100) was significantly lower than that of the other men in the sample ($p < 0.001$).

In all of the samples there was a significant enhancement of risk when two or more major indicators of myocardial disease were present. When "definite" or "probable" ischemic heart disease was associated with "definite" or "probable" LVH patterns on the electrocardiogram, the risk was 31.0 per 100 in 5 years; combined with cardiac dilatation ≥ 2 SD, the risk was 41.4 per 100; and combined with present or past evidence of congestive heart failure the risk was 31.0 per 100 (53.3 per 100 in the random samples).

Chronic Disorders of Heart Rate, Rhythm, Conduction, and Repolarization as Risk Factors for Arrhythmic Death in 5 Years

Disorders of heart rate, rhythm, conduction, and repolarization were widely prevalent in the random samples. As single variables, major disorders in each of these categories, including sustained tachycardia, sustained bradycardia, disorders of the pacemaker, prolonged QRS conduction, prolonged repolarization, and very frequent supraventricular premature complexes, were associated with a significantly enhanced risk of arrhythmic death (TABLE 3).

One or more ventricular premature complexes (VPCs) were found in the tape recordings at the initial examinations of 71.6% of the men in the random samples. The arrhythmic death rate among these men (6.0 per 100 in 5 years) was higher than that of men without any VPCs (2.5 per 100), but the difference was of borderline significance ($p < 0.1$). After classification of the men by

TABLE 2

RANDOM SAMPLES:
CLINICAL EVIDENCE OF MYOCARDIAL DISEASE AT INITIAL EXAMINATION

	Men at Risk *		Deaths in 5 Years			
			Arrhythmic * (n=38)		Circulatory Failure * (n=32)	
	No.	%	%	Rate per 100	%	Rate per 100
All men in random samples	687	100	100	5.5	100	4.7
Clinical evidence of ischemic heart disease	139	20.8	51.3	13.7	15.6	3.6
"Definite" ischemic heart disease † ‡	103	15.0	44.7	16.5 §	12.5	3.9
"Probable" ischemic heart disease #	36	5.2	5.3	5.6	3.1	2.7
"Possible" ischemic heart disease ¶	81	12.8	14.7	6.1	10.3	3.7
LVH patterns on electrocardiagram	116	17.4	31.4	9.5	16.1	4.3
"Definite" and "probable" **	27	4.1	17.1	22.2 ‡	6.5	7.4
"Possible" ††	89	13.4	14.3	5.6	9.7	3.4
X-Ray evidence of dilatation ‡‡	62	9.9	24.2	12.9	7.1	3.2
≥2 SD above expected value	15	2.4	12.1	26.7 ‡	0.0	0.0
≥1 SD but <2 SD above expected value	47	7.5	12.1	8.5	7.1	4.2
Definite clinical evidence of congestive heart failure §§	18	2.6	21.1	44.4 ‡	3.1	5.6
Men with none of the above	313	49.4	13.5	1.6	41.1	3.8

* See the first three footnotes in TABLE 1.

† References 2 and 4.

‡ Definite or probable myocardial infarction, electrocardiographic evidence of myocardial infarction, definite coronary insufficiency, or definite angina pectoris.[2, 4]

§ $p < 0.005$ (see NOTE in TABLE 1).

Probable angina pectoris or coronary insufficiency, ischemic S-T segments or T waves on standard electrocardiogram.[2, 4]

¶ Electrocardiographic evidence of possible myocardial infarction; transient "ischemic" S-T segments on tape recordings.[2, 4]

** Voltage and S-T segment and T wave abnormalities.[2, 5]

†† Voltage only.[2, 5]

‡‡ From insurance tables, based on height and weight.[2, 6]

§§ Reference 2.

TABLE 3

RANDOM SAMPLES
CHRONIC DISORDERS OF HEART RATE, RHYTHM, CONDUCTION, AND REPOLARIZATION
AT INITIAL EXAMINATION

	Men at Risk *		Deaths in 5 Years			
			Arrhythmic * (n=38)		Circulatory Failure * (n=32)	
	No.	%	%	Rate per 100	%	Rate per 100
All men in random samples	687	100	100	5.5	100	4.7
Disorders of heart rate	16	2.7	12.5	25.0 †	0.0	0.0
Sustained tachycardia	14	2.3	9.4	21.4	0.0	0.0
Sustained bradycardia	2	0.3	3.1	50.0	0.0	0.0
Disorders of pacemaker	82	4.8	20.6	21.9 †	3.4	5.5
Atrial fibrillation	2	0.3	2.9	50.0	0.0	0.0
Ectopic or shifting atrial rhythms	19	2.8	11.8	21.1	0.0	0.0
A-V junctional rhythms	11	1.6	5.9	18.2	3.4	9.1
Supraventricular dysrhythmias SPCs ≥10/1000 complexes	40	6.5	15.6	12.5 ‡	14.3	10.0
Disorders of conduction QRS >0.11 sec	27	4.1	14.3	18.5 §	6.5	7.4
LBBB	5	0.8	5.7	40.0	3.2	20.0
RBBB	18	2.7	8.6	16.7	3.2	5.6
Ventricular dysrhythmias						
Any VPCs	435	71.6	86.7	6.0 ‡	64.3	4.1
VPCs ≥10/1000 complexes	61	10.0	26.7	13.1 §	3.6	1.7
Q form VPCs	146	24.0	53.3	11.0 †	28.5	5.5
Early-cycle VPCs R-R′/Q-T_e <1	43	7.1	26.7	18.6 †	10.7	7.0
VPC pairs	81	13.3	13.3	4.9	0.0	0.0
Paroxysmal ventricular rhythms	29	4.8	10.0	10.3	3.6	3.4

Q-T_c (Bazett) $\geq$440 msec ‖	46	6.9	14.2	15.2 §	10.0	6.5
Men with none of the above	194	32.4	9.4	1.5	14.8	2.1

NOTE: A-V=atrioventricular; LBBB=left bundle branch block; RBBB=right bundle branch block; SPCs=supraventricular premature complexes; VPCs=ventricular premature complexes.

* See first three footnotes in TABLE 1.

† $p < 0.005$.

‡ $p < 0.1$ (see NOTE in TABLE 1).

§ $p < 0.01$.

‖ Reference 23.

the mean frequency of VPCs per 1000 complexes in the 24-hour recordings at the initial examinations, it was found that in all samples the risk of arrhythmic death increased stepwise as VPC frequency increased on a logarithmic scale, from <0.01 VPC/1000 complexes (arrhythmic death rate 2.3/100 men in 5 years in random samples) to >10 VPCs/1000 complexes (arrhythmic death rate 13.1/100 men in 5 years in random samples).[7] Men whose tape recordings contained VPCs at a frequency >1/1000 complexes had a subsequent risk of arrhythmic death that was significantly higher than that of all other men in the sample.

The frequency of bigeminal and trigeminal ventricular rhythms, paired VPCs, brief runs (1–15 complexes) of paroxysmal ventricular rhythms, and multiformal VPCs (two or more forms) increased with the frequency of all VPCs. When the effect of VPC frequency on risk of arrhythmic death was taken into account, no risk was added when complex VPCs were present.[7]

After classification of all VPCs by form, based on the configuration in the bipolar chest lead that was used for the recording (which had the positive electrode over the fifth rib in the nipple line), it was found that VPCs with a QS configuration in this lead were associated with a significantly enhanced risk of arrhythmic death ($p < 0.01$). Many of these VPCs probably originated in the left ventricle. They were present in 38.8% of all recordings. The risk associated with "Q form" VPCs was independent of VPC frequency. When multiformal VPCs were present in a recording, there was no added risk of arrhythmic death when the effects of VPC frequency and the presence of Q form VPCs were taken into account.

The presence of "early-cycle" VPCs in which the QRS complex of the VPC encroached upon the T wave of the preceding complex (R-R′/Q-T < 1) was associated with a significantly enhanced risk of arrhythmic death ($p < 0.001$). This risk was independent of VPC frequency and of VPC form.

A multiple logistic regression, including only the ventricular dysrhythmia variables mentioned earlier, indicated that among these variables only VPC frequency, Q form, and early-cycle VPCs contributed to risk of arrhythmic death independently of any risk associated with other dysrhythmia variables.[7]

The prognostic significance of ventricular dysrhythmias was significantly enhanced by the presence of definite or probable clinical evidence of ischemic heart disease (TABLE 4). In the absence of clinical evidence of ischemic heart disease, the risk of arrhythmic death associated with frequent VPCs, or with paroxysmal ventricular rhythms, was no greater than that of men with no VPCs at all. The risk of arrhythmic death associated with Q form VPCs and with early-cycle VPCs was higher in the presence of ischemic heart disease; but, even in the absence of ischemic heart disease, men with Q form VPCs and early-cycle VPCs had an arrhythmic death rate significantly higher than that of other men with VPCs.

Conditions Under Which Arrhythmic Deaths and Deaths in Circulatory Failure Occurred

Chronic Myocardial Disease Present Prior to Death

The men in these samples were examined one to seven times in the interval between their initial examination and their deaths, and information about them was obtained from physicians' records and from hospital records.

At the last examination prior to arrhythmic death, 92.5% of men in the random samples had clinically detectable chronic myocardial disease. Seventy-two and six-tenths percent had symptomatic or clinically evident chronic ischemic heart disease, 40% had LVH patterns on the electrocardiogram, 22.5% had cardiac dilatation on chest X-ray film, and 45% had evidence of chronic congestive heart failure. At autopsy, myocardial hypertrophy (80.0%) was as frequent as occlusive coronary arteriosclerosis (70.0%).[8]

In the random samples 51.6% of men who subsequently died in circulatory failure also had clinically detectable myocardial disease, but the number of men with manifestations in each category was smaller, fewer men had multiple manifestations, and a significantly larger proportion (48.4%) had no manifestations of myocardial disease.

TABLE 4

VENTRICULAR DYSRHYTHMIAS: EFFECT OF PRESENCE OF ISCHEMIC HEART DISEASE ON RISK OF ARRHYTHMIC DEATH

	"Definite" or "Probable" Ischemic Heart Disease			
	Present		Absent	
	Men at Risk (No.)	Arrhythmic Deaths (Rate per 100)	Men at Risk (No.)	Arrhythmic Deaths (Rate per 100)
VPCs $\geq$ 10/1000 complexes	38	28.9 *	54	5.6
Q form VPCs	121	19.8 *	146	6.8 †
Early-cycle VPCs, R-R′/Q-T $<$1	22	40.9 †	40	15.0 *
Paroxysmal ventricular rhythms	29	31.0 †	26	3.8

NOTE: Probabilities of higher rates among men with ischemic heart disease (IHD) are based on comparison with the rates of similar men without IHD; probabilities of higher rates of men without IHD are based on comparison with rates of similar men without VPCs.

† $p < 0.05$.

* $p < 0.005$.

Acute Myocardial Disease at the Time of Death

In the random samples, 62.5% of men who had arrhythmic deaths, and 100% of men who died in circulatory failure had developed clinical evidence of acute abnormal conditions affecting the myocardium over a period of hours, days, or weeks immediately prior to death. The manifestations that preceded the two kinds of deaths were quite different.[8]

Sixty percent of men who experienced arrhythmic deaths had acute ischemic heart disease at the time of death. This was symptomatic in 35.3% of the cases and was "silent" (not reported by the subject and not suspected by his associates) in 22.5% of cases. In the "silent" cases it was represented by a recent acute myocardial infarction or coronary thrombosis discovered at autopsy. Only 3.2% of men who died in circulatory failure had symptomatic acute ischemic heart disease and no "silent" acute lesions were found at autopsy.

Ten percent of men who had arrhythmic deaths experienced prior exacerbations of chronic congestive heart failure. This was subacute in all cases and clinically "severe" (disabling) in only 2.5% of cases. Evidence of peripheral circulatory failure (shock) was present at the time of death in only 10% of men with arrhythmic deaths and was not severe in any case. On the other hand, 68% of deaths in circulatory failure were preceded by exacerbations of congestive heart failure, of which 8% were acute and 26% severe; and 100% of these deaths occurred in the setting of severe shock.

Evidence of acute anoxemia affecting the myocardium and arising from causes other than ischemic heart disease was present at the time of 25% of arrhythmic deaths. In 22.5% of the cases this was anoxic and was caused primarily by acute exacerbations of severe chronic obstructive pulmonary disease. Anoxic anoxemia, caused by central respiratory failure from stroke or brain tumor, or by obstructive respiratory failure from carcinoma of the lung, pneumonia, congestive heart failure, or acute airway disease was present at the time of death in 48% of men dying in circulatory failure. All of the hearts of men who died in circulatory failure were considered to have been anoxemic as a result of the profound circulatory collapse that was present at the time that the ventricular contractions ceased.

A larger proportion of the men who died arrhythmic deaths (57.5% as contrasted with 25.8%, $p < 0.01$) were receiving medications that had cardiac effects (such as digitalis glycosides, quinidine, other antiarrhythmic medications, vasodilators, antihypertensive agents, or diuretics) before the onset of the terminal illnesses. The only single category of medication which was associated with a greater than expected number of arrhythmic deaths was digitalis glycosides (30.0% versus 9.7%, $p < 0.05$).

Uremia (blood urea nitrogen level up to 41 mg/dL) was present prior to 5% of the arrhythmic deaths. Severe metabolic derangements were a feature of many of the terminal illnesses that preceded death in circulatory failure.[8]

Chronic Disorders of Rate, Rhythm, Conduction, and Repolarization Prior to Death

In the random samples, 92.5% of men who experienced arrhythmic death had chronic disorders of heart rate, rhythm, conduction or repolarization, and 51.6% of men who died in circulatory failure had similar abnormalities at the last examination prior to death. In every category except supraventricular dysrhythmias and prolonged repolarization, the abnormalities were significantly more frequent among men who died arrhythmic deaths. The single abnormalities that most significantly distinguished between the two kinds of subsequent death were early cycle VPCs ($p < 0.01$), sustained tachycardia ($p < 0.05$), episodes of sinus delay ($p < 0.05$), and Q form VPCs ($p < 0.1$) in that order.[8]

In the high-risk sample, for which the men were selected partly on the basis of preexisting disorders of rhythm and conduction, the only one of these variables that distinguished between arrhythmic death and death in circulatory failure at the last examination prior to death was sinus delay ($p < 0.01$). There was no overall difference with respect to the prevalence of any other variable. Although a greater proportion of the men with arrhythmic death had preceding supraventricular dysrhythmias, there was no significant difference between them and the men who died in circulatory failure with regard to any single kind of

supraventricular dysrhythmia. A relatively larger proportion of the men who died in circulatory failure had evidence of prolonged repolarization shortly before death ($p < 0.1$).

Central Nervous System Arousal, Position and Activity of the Subjects Immediately Prior to Death

With the exception of those who were under anesthesia at the time of death, all of the men in these samples who experienced arrhythmic death were awake, or asleep and arousable, immediately before they collapsed and ventricular contractions ceased, whereas all of the men who died in circulatory failure were comatose and not arousable. Sixty-five and nine-tenths percent of men who experienced arrhythmic death were actively mobile, standing or sitting, at the time that they collapsed. All of the men who died in circulatory failure were lying immobile before the ventricular contractions ended.[8]

Precipitating Events

In all of the samples, 17.1% of the men with arrhythmic death collapsed while engaged in activities that are known to be associated with vagal effects upon the heart and have been reported to be associated with the onset of dysrhythmias.[9-14] Thirty-four and one-tenth percent of the arrhythmic deaths occurred during or immediately (<5 min) after the subject had been engaged in activities known to be associated with the occurrence of myocardial ischemia or with sympathetic effects upon the heart, such as tachycardia, or with an increase in ventricular dysrhythmias. All of these activities have also been reported to be associated with the occurrence of fatal arrhythmias.[14-18] Fourteen and six-tenths percent of arrhythmic deaths occurred within a period of a few minutes to not more than 4 hours after the onset of pain and other symptoms of acute myocardial ischemia.

In all of the samples, 86.5% of the deaths in circulatory failure were precipitated by conditions that led steadily and promptly (within minutes, hours, or a few days) to collapse of the peripheral circulation, and 13.5% of these deaths were precipitated by conditions that led promptly to myocardial failure.[8]

Mechanism of the Fatal Arrhythmia

We have observed four mechanisms by which sudden fatal (or potentially fatal) ventricular arrhythmias have occurred in men without prior collapse of the circulation: (1) An early-cycle VPC falling in the vulnerable period of repolarization and initiating ventricular fibrillation. This occurred immediately after physical activity that produced a sinus tachycardia of 165/minute.[17] (2) A marked widening of the Q-T interval during a symptomatic episode of myocardial ischemia, with an early cycle R-on-T VPC initiating ventricular fibrillation. (3) The apparently spontaneous appearance of a ventricular escape rhythm after a long R-R interval during a period of bradycardia, with rapid degeneration of the rhythm to ventricular fibrillation. This occurred in a man with a recent acute myocardial infarction. (4) A very rapid supraventricular

tachycardia occurring during sleep, leading directly to the initiation of a rapid ventricular rhythm terminating in ventricular fibrillation.

Summary and Conclusions

In these random samples of middle-aged American men, 91% of the deaths within 1 hour and 85% of the deaths within 24 hours were precipitated by the sudden occurrence of a cardiac arrhythmia at a time when the peripheral circulation had not collapsed and was still adequate to support the function of the brain.

The multivariate analyses of the large number of highly interrelated variables from the first examination that represent potential risk factors for arrhythmic death in 5 years are still under way. The initial results reported here, based largely on single variable analyses, indicate that the most significant risk factors fall into four categories:

1. *The major noncardiac risk factors for ischemic heart disease—hypertension, cigarette-smoking, and elevated serum cholesterol.* These risk factors are widely prevalent in these samples. Hypertension and cigarette-smoking show a gradient of risk which increases with the severity of hypertension and with the number of cigarettes now being smoked, but only very frequent cigarette-smoking carried with it a relatively high degree of risk. An elevated serum cholesterol level was related to risk of death in circulatory failure caused by stroke or peripheral vascular disease but not to arrhythmic deaths.

2. *Other noncardiac risk factors for arrhythmic death.* These are not major risk factors for ischemic heart disease in younger people and are not highly prevalent in the sample. Among these, diabetes mellitus was related to deaths in circulatory failure as well as to arrhythmic death, and may be related to mortality in general. Evidence of arteriosclerosis of other vessels was probably an indicator of underlying and asymptomatic arteriosclerosis of the coronary arteries, which is frequently found at autopsy in arrhythmic deaths. Elevated serum uric acid levels may be related to chronically high levels of central nervous system arousal.[19] A heavy intake of alcoholic drinks was strongly associated with heavy cigarette-smoking and with chronic obstructive pulmonary disease, but alcohol also is toxic to the myocardium and it is sometimes arrhythmogenic.[20] Chronic obstructive pulmonary disease with severe airway disease was a risk factor by virtue of its frequent association with the subsequent development of acute respiratory obstruction and anoxic anoxemia.

3. *Evidences of chronic myocardial disease.* These were the most potent risk factors for arrhythmic death in these samples. Ischemic heart disease, LVH patterns on the electrocardiogram, evidences of cardiac dilatation, and congestive heart failure all carried with them a high risk of arrhythmic death. For each of the conditions, the risk became higher as the condition was more overt and advanced and as the evidence for it was more "definite." "Probable" or "possible" ischemic disease, "probable" LVH patterns, and cardiac dilatation >1 SD above the expected (but <2 SD), carried with them a risk of arrhythmic death that was only slightly higher than the average risk of all men in the samples, although it was significantly higher than the risk of men with no myocardial disease. Combinations of ischemic heart disease with LVH patterns, cardiac dilatation, or congestive heart failure increased risk significantly; but LVH patterns, cardiac dilatation, and congestive heart failure also appeared to

be associated with increased risk independently of the presence of ischemic heart disease.

4. Disorders of heart rate, rhythm, conduction, and repolarization. Several kinds of these disorders were, as single variables, associated with a high risk of arrhythmic death. These variables were highly correlated and the extent to which they made independent contributions to risk is still to be ascertained. Among the ventricular dysrhythmia variables, which have been studied intensively,[7] only VPC frequency, Q form VPCs, and early-cycle VPCs made contributions to risk that were independent of those associated with the other ventricular dysrhythmias. The risk associated with ventricular dysrhythmias was strongly influenced by the presence of ischemic heart disease. In the absence of ischemic heart disease, the risk associated with frequent VPCs or with episodes of paroxysmal ventricular rhythms was not significantly different from that of men in the samples who had no ventricular dysrhythmias; but the risk of men with Q form VPCs and early-cycle VPCs was significantly higher than that of men with no VPCs, even in the absence of clinical evidence of ischemic heart disease.

In the interval between the initial examination and death, many men developed new manifestations of heart disease. At the time of death the great majority of those who died arrhythmic deaths had preexisting myocardial disease, but this was often asymptomatic. As the data from the nationwide survey had indicated, only 72% of the men who died arrhythmic deaths had previous clinically evident coronary heart disease. However, 92.5% of these men had been found at examination to have detectable clinical evidence of chronic myocardial disease prior to death. This myocardial disease included LVH patterns, cardiac dilatation, and chronic congestive heart failure as well as evidence of ischemic heart disease. At autopsy, hearts that were hypertrophied were almost as prevalent among these men (80%) as occlusive lesions of one or more major coronary vessels (70%).

One-half of the men in the random samples who died in circulatory failure had no clinical evidence of prior myocardial disease, but the other half had chronic myocardial disease similar to that of the men who experienced arrhythmic deaths. Some men with severe and far-advanced chronic myocardial disease died in circulatory failure, but in general the myocardial disease among these men was not so far advanced as that which was found in the men with arrhythmic deaths. There was only one man who had an arrhythmic death who did not have preceding clinical myocardial disease. All of the other men who had no clinical evidence of chronic myocardial disease died in circulatory failure.

Both arrhythmic deaths and deaths in circulatory failure usually occurred in the setting of an acute myocardial disorder that had developed within minutes, hours, or days immediately prior to death. The acute disorders that preceded the two kinds of deaths were different.

The majority of arrhythmic deaths occurred in the setting of acute ischemic heart disease or of myocardial anoxemia from other causes. In the random samples 60% of the arrhythmic deaths occurred in the setting of an episode of acute ischemic heart disease which was asymptomatic in 22.5% of the cases and took the form of a "silent" acute myocardial infarction or coronary occlusion found at autopsy. The proportion of "silent" myocardial infarctions in this series is like that which has been reported from Seattle and Miami.[21, 22] In addition, at least 70% of the arrhythmic deaths occurred in a setting of acute myocardial anoxemia from causes other than ischemic heart disease—chiefly anoxic

anoxemia caused by acute exacerbations of chronic obstructive pulmonary disease, but in a few cases anemic anoxemia caused by severe chronic anemia.

In the random samples only 3.2% of the deaths in circulatory failure occurred in the setting of acute ischemic heart disease. Such deaths occurred, rather, in the setting of profound circulatory collapse ("shock"), and 68% of them occurred also in the setting of acute or subacute and severe exacerbations of congestive heart failure. The acute myocardial anoxemia and other metabolic abnormalities that undoubtedly affected the myocardium at the time of death in circulatory failure appeared to be primarily the result of failure of the general circulation.

The simple presence, absence, or frequency of chronic disorders of heart rate, rhythm, conduction, or repolarization at the last examination prior to death was not the final determinant of whether or not an arrhythmic death would occur. In the random samples a larger proportion of the men who died arrhythmic death had significant chronic ventricular dysrhythmias, sustained bradycardia or tachycardia, abnormal supraventricular rhythms, or prolonged QRS conduction; but this was not the case in the high-risk sample. In the high-risk sample, immediately prior to death, the men who died in circulatory failure exhibited all of the kinds of chronic disorders of rhythm and conduction that were exhibited by the men who died arrhythmic death, and, in general, these were equally prevalent.

The functional state of the central nervous system immediately prior to death was of great importance in determining the kind of death that would occur. Most of the arrhythmic deaths occurred in men who were awake, and often active and aroused. These deaths were in many cases precipitated by activities or conditions known to be accompanied by autonomic nervous effects—vagal or sympathetic—on cardiac function. The acute fatal arrhythmias that were observed to occur in these cases were initiated by mechanisms that might readily have been set in motion by the kinds of neural stimulation or the acute myocardial ischemia that was present at the time of the arrhythmic deaths.

Deaths in circulatory failure occurred in men who were unconscious and unarousable. The chain of events that led to these deaths was set in motion when the subject was conscious by acute events that led to circulatory collapse and unconsciousness—a major hemorrhage, trauma, or stroke for example. When such an event occurred in a man who had very severe or even acute myocardial disease accompanied by major abnormalities of rhythm and conduction, and who might therefore have been expected to die an arrhythmic death, the end result was not an arrhythmic death but a death in circulatory failure. This was true in all cases, except in those in which the subject was under anesthesia and an acute arrhythmia was precipitated by tracheal intubation.

The importance of the precipitating event in determining the nature of the fatal outcome places serious limits upon the extent to which the occurrence of an arrhythmic death can be predicted in advance from information based only upon features of the subject or his activities 5 years prior to the event.

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Discussion

Dr. Lockhart (*New York, New York*): Did you notice any difference in risk between the VPCs that were occurring during the day with activity versus VPCs constantly through the day?

Dr. Hinkle: I haven't examined that in great detail. My impression is that there is no difference.

Dr. D. P. Zipes (*University of Indiana, Indianapolis, Indiana*): I was intrigued by the Q in the PVC that you presented. Do you think that this is a different electrophysiologic mechanism that may be associated with an increased risk of sudden death? Or do you think it represents or marks a different patient, such as one who might have had an anteroseptal versus an inferior myocardial infarction?

Dr. Hinkle: You know how difficult it is to say anything about VPCs from a single lead of a tape recording. My general thinking is that the latter of the two probabilities is the correct one. I think that we find these Q forms associated more with severe lesions of the left ventricle.

Dr. R. Crampton (*University of Virginia, Charlottesville, Virginia*): I was interested, but a little confused, about the predictive powers that you assign to the corrected Q-T intervals in sudden death in your population. Several studies in patients with acute myocardial infarction have shown that the Q-T interval is a predictor of ventricular fibrillation or ventricular tachycardia in the first 24 hours. We have done a prospective study in a very small group of patients. If we see an individual within 3 hours of onset of pain, a lengthened Q-T interval will predict ventricular tachycardia. None of the patients in our study died, so we can't say anything about predicting mortality. So how should we weight the Q-T interval within your population as a predictor?

Dr. Hinkle: In those of the 687 men who in random samples had a prolonged Q-T interval, it was not shown to be a very strong predictor of sudden death. It is really not a very important indicator, even if you see it in persons at the last examination before death.